REMARKS

Claims 8-22 are currently pending. Claims 8-22 have been rejected.

Response to Specification Objection under 35 U.S.C. §132

Applicants acknowledge that the Examiner agreement that the recitation "25µl of Detection Reagent 1" does not constitute an amendment to the specification and does not introduce new matter.

Applicants also acknowledge the withdrawal of the objection of the recitation "to calibrators and cellular RNA" in view of the deletion of the recitation.

The Examiner has maintained the objection to the recitation of "isolated and" at page 23, line 14. Applicants do not agree that this phrase adds new matter. However, in order to expedite prosecution of the instant application, applicants have deleted the objected phrase. Reconsideration and withdrawal of the objection under 35 U.S.C. §132(a) is respectfully requested.

Response to Claim Rejections under 35 U.S.C. §112

Claims 8-22 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which allegedly does not enable one skilled in the art how to make and use the invention. More particularly, the Examiner contends that the instant application and data presented in the Declaration do not enable the claims because there is allegedly a lack of correlation between HPV16 and any other HPV type; and the amount of experimentation needed to practice the claimed invention is allegedly undue. Applicants respectfully disagree with this rejection.

Applicants assert that (1) different high risk HPV types may be used to diagnose high risk HPV-induced disease; (2) there is a correlation among the high risk HPV types; and (3) there is a correlation between high risk HPV gene transcript ratios and high risk HPV-induced disease. Applicants further assert that the claims are fully enabled as the disclosure teaches one skilled in the art how to make and use the assays for screening purposes in patients.

In the instant specification, the described method relating to HPV 16 also applies to other high risk HPV types, such as but not limited to, HPV 18 and HPV 31. Cells having high risk HPV types are known to lead to cancer. As described in Koromilas, et al. (*See*, Exhibit 13 of Declaration) high risk HPV types include HPV types 16, 18, and 31. Koromilas further indicates that E6 and E7 viral genes are consistently expressed and are critical for the development of malignant transformation. Similarly, Stoler, et al. (*See*, Exhibit 5 of Declaration) describes the different risk types of HPV which also includes high risk HPV 16, 18, and 31 to name a few. Stoler also associates active transcription of HPV DNA with cervical neoplasia and the expression of the E6 and/or E7 regions. These publications demonstrate what was known in the art and the predictability with respect to the different high risk HPV types.

The instant specification provides working examples of high risk HPV 16 and the Lorincz Declaration additionally provides support for high risk HPV 18 and 31, as examples of the claimed genus. The legal standard for claiming a genus is whether a person skilled in the art would understand that the inventor had possession of the claimed genus. *See, e.g., Capon v. Dudas*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). However, it "is not necessary for every permutation within a generally operable invention to be effective for an inventor to obtain a generic claim, provided the effect is sufficiently demonstrated to characterize a generic invention." *Id.* at 1359. Furthermore, the court felt that the specification's disclosure of two species was enough to support claims covering the genus for entire species in *Amgen Inc. v. Hoechst Marion Roussel*. 314 F.3d 1313, 1332 (Fed. Cir. 2003) (holding the specification's disclosure of two species of EPO was sufficient to claim the entire genus of vertebrate EPO).

The instant specification describes a method of diagnosing high risk HPV-induced disease. In particular, applicants present examples of HPV 16, 18, and 31. However, each and every possible species need not be described in order to obtain a generic claim. The Examiner contends that

> [t]he fact that multiple HPV types are associated with cervical cancer and that multiple HPV types have "similar expression patterns" would not lead a skilled artisan to conclude that the particular ratios of the instant claims could be relied upon in the diagnosis of disease caused by HPV types other than HPV 16. (Office Action- page 5)

Applicants respectfully disagree with the Examiner's contention. However, from the instant specification, the confirmatory Lorincz Declaration, and factors including knowledge in the field at the time of filing, all support generic claims to the claimed method of diagnosing high risk HPV-induced disease.

As mentioned above, the correlation between different high risk HPV types and the association of active transcription of high risk HPV DNA with cervical neoplasia and the expression of E6 and/or E7 regions provide the nexus that the ratios of genes correlate to expression ratios of other high risk HPV types. Applicants assert that the instant specification enables the claimed methods without undue experimentation.

The Office Action further indicates that, "the examiner has not rejected the instant claims for a lack of utility, but rather for a lack of enablement" (Office Action- page 7). However, the courts conflate the enablement analysis of 35 U.S.C. §112 with proof of utility under 35 U.S.C. §101. *See, e.g. In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (the court's analysis of utility under 35 U.S.C §101 satisfied enablement requirements). As interpreted by the courts, an enabling disclosure must teach a person skilled in the art without undue experimentation. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Both usefulness and enablement in patent law includes the expectation of further research and development. *Brana* at 1568, quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961).

The Examiner contends that it is unpredictable whether a ratio of gene transcripts would be detectable in a patient, whether such a ratio in a patient would correlate to a disease stage, and what disease stage such a ratio in a particular patient would include. Clinical data is not necessary to support enablement for pharmaceutical compounds. *Brana,* 51 F.3d at 1567-68. As the court made clear, requiring full and complete human studies to prove utility and enablement for patents of pharmaceutical products would be cost-prohibitive and hinder research. *Id.* at 1567-1568 (quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961)). Specifically, the court has held that "Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) (holding complete human testing is not necessary for a patent on a prosthetic device). Rather, the full safety and effectiveness is "more properly left to the Food and Drug Administration (FDA)." *Id.* An inventor who "taught the public a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a

significant and useful contribution to the art" thereby, providing adequate proof of utility and enablement. *Brana* at 1567-68, quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961).

According to MPEP: 2164.02, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. A rigorous or an invariable exact correlation is not required." The applicants have shown a correlation between cell line models, such as W12, HaCaT, and SiHa, and cancer in a human patient and evidence that such cell lines are universally recognized by researchers as model systems of human epithelium in a patient at various states progressing to HPV 16- induced cancer. One skilled in the art would correlate the fact that established cell line models used in HPV 16-induced cancer would also be useful in diagnosing other HPV- induced cancers. Furthermore, HeLa cells are an immortal cell line commonly used in medical research, where the cell line was derived from cervical cancer cells obtained from a female patient. Similarly, the neoplastically transformed cell lines LKP31 and A31 represent cancerous cells. The methods described in the instant specification which involves quantifying levels of HPV mRNA from a sample and determining the ratio of the genes of interest, as exemplified using HPV 16, and further confirmed by HPV 18 and HPV 31, provide sufficient guidance for one skilled in the art to quantify and determine the ratio of the genes of interest, such that the disease stages could be determined.

The Lorincz Declaration confirms the description in the instant specification regarding gene expression of high risk HPV types other than HPV 16. Specifically, in the HeLa cell line, the E6-E7/L1 mRNA ratio of 9.5 correlates to high risk HPV-induced cell transformation, neoplasia, neoplastic onset, disease and cancer. Similarly, with respect to HPV 31, the Declaration confirms that the HPV 31 E6-E7/L1 mRNA ratio is 11.7 and 8.4 for both neoplastically transformed cell lines, LKP31 and A31, respectively, correlates to high risk HPV-induced cell transformation, neoplasia, neoplastic onset, disease and cancer. For example, the LKP31 cell line is a well established cell line derived from human foreskin keratinocytes transfected and immortalized with the HPV 31 genome. In fact, the resulting ratios for both HPV 18 and HPV 31 have E6-E7/ L1 mRNA ratios greater than 2 and greater than 4 which correspond to the HPV-induced disease stages. The cell lines that are used in these experiments represent *in vivo* conditions. The high risk HPV types exemplified in the instant specification and further confirmed by the Lorincz Declaration provide guidance for one skilled in the art who recognizes that different high risk

HPV strains have similar gene expression patterns. The prior art has established that the high risk HPV types, for example, HPV 16, 18, and 31, are etiological agents of many cancers, including those of the cervix. Therefore, the HPV 18 and 31 examples result in ratios that are indicative of high risk or onset of HPV-induced cancer. Contrary to the Examiner's contention, applicants have demonstrated through the prior art and instant specification, and further confirmed in the Lorincz Declaration, that the expression of viral oncogenes correlate to disease. The MPEP 2164.02 supports the fact that:

> An applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Qugg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)...The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejection all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108, USPQ 321, 325 (CCPA 1956)).

The Examiner has asserted that the cited prior art references do not show changes in the ratios of various genes as claimed. The data provided in the specification and confirmatory declaration in combination with the prior art show the ratios in three separate high risk HPV types to be correlative to disease stages. The references demonstrate that one skilled in the art would recognize that different HPV strains have similar gene expression patterns. Upon reading the instant application, the skilled artisan would understand that the claimed invention could be readily used for other high risk HPV strains. The references discussed in the Lorincz Declaration thereby demonstrate the level of knowledge in the field.

One must consider what is already known in the field for the "predictability of the science" factor of enablement. The references discussed in the Lorincz Declaration demonstrate that one skilled in the art recognizes that high risk HPV strains have similar gene expression characteristics. Therefore, the skilled artisan would expect similar results when quantifying and determining the ratio for other high risk HPV types. Because "patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." (*In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991), and in view of "[t]he fact that some experimentation is necessary does not preclude enablement as long as the amount of experimentation is reasonable given the nature of the invention and the state of the art. (*Boston Scientific Scimed, Inc. v. Cordis Corp.*, 2005 U.S. Dist. LEXIS 23612 (D. Del., October 14, 2005 at *13), the

instant specification teaches how to make and use the claimed assays. Furthermore, a generic claim is enabled as long as the "disclosure teaches those skilled in the art what the invention is and how to practice it." (*In re Grimme*, 124 USPQ at 502.). Thus, the skilled artisan can readily practice the invention with any high risk HPV species by following the teachings of the instant application of high risk HPV 16, and in view of his awareness of the knowledge in the HPV field. Therefore, the invention as claimed is fully enabled.

The Examiner has rejected the claims for lack of enablement because the applicants have not shown whether a ratio might be detected in a patient, whether the ratio would correlate to a disease stage in a patient, and what disease state the ratio in a patient would indicate. As previously discussed, clinical studies are not required in order to show enablement. The requirement for enablement is a disclosure that teaches how to make and use the claimed assays for screening purposes. The instant specification describes cell samples, methods for measuring the levels of gene expression in a gene of interest, such as HPV E6, E7, L1, E4, and E2 genes, guidelines as to what disease stage a particular ratio value correlates with, and provides sufficient guidance for one of skill in the art to make and use the claimed assays for screening purposes in patients.

In summary, applicants have presented general teachings of how to identify HPV diseases in patient samples and also specific examples of the identification using *in vitro* models identifying high risk HPV-induced disease, further confirmed by the Lorincz Declaration exemplifying other high risk types. Given the knowledge within the field as shown in the cited prior art references, one skilled in the art would be able to use the information provided in the specification to make and use the claimed invention without undue experimentation. Reconsideration and withdrawal of this §112, first paragraph rejection is respectfully requested.

CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. The applicant respectfully submits that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested.

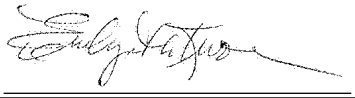
Applicants would like to hold a telephone conference with the Examiner at her earliest convenience in order to facilitate examination and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 2629-4005US4.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 2629-4005US4.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: September 1, 2006 By: 

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